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Common and distinct neural mechanisms associated with the conscious experience of vicarious pain

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Abstract:

Vicarious pain perception has been an influential paradigm for investigating the social neuroscience of empathy. This research has highlighted the importance of both shared representations (i.e. involved in both experiencing first-hand physical pain and observing pain) and mechanisms that discriminate between self and other. The majority of this research has been conducted in healthy younger adults using a group-average approach. There are, however, known inter-individual differences that can contribute to vicarious experience. One factor relates to the degree to which individuals experience reportable pain-like sensations/feelings in response to seeing others in pain. Here we conduct the first systematic investigation of the neural basis of conscious vicarious pain in a large sample of participants. Using cluster analysis, we firstly demonstrate that consciously experiencing the pain of others is surprisingly prevalent and, exists in two forms: one group experiences sensory and localised pain whilst the other group report affective and non-localised experiences. Building on this, we used electroencephalography (EEG) and structural brain imaging to examine the neural correlates of vicarious pain in the three different groups. We find that the dominant electrophysiological marker used to index vicarious pain in previous studies (mu and beta suppression) was only found to be significant in the sensory and localised pain responder group (with a sensitive null result in the ‘neurotypical’ group). Finally, using voxel-based morphometry we identify a common differences in the two pain responder groups relative to typical adults; namely increased grey-matter in insula and somatosensory cortex and reduced grey matter in the right temporal-parietal junction (rTPJ). We suggest that the latter reflects a reduced ability to distinguish bodily self and other, and may be a common factor distinguishing conscious from unconscious vicarious experience.

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Introduction

Our capacity to share the experiences of others is a critical aspect of human social behaviour.

One characteristic considered to be important to this process is the ability to match observed states of

other people onto representations of our own body. This process has been referred to under several names in the literature including empathy, simulation, contagion, and vicarious perception / experience. There is now good evidence of a near universal tendency for humans to vicariously perceive the actions, emotions, and sensations displayed by others. This evidence has most commonly been provided by human brain imaging experiments that have shown that passively observing experiences (e.g. touch, pain, disgust, actions) recruits similar brain regions to those that become active when we experience the states ourselves (Molenbergh *et al.* 2012). While most of us do not feel pain when observing pain to others, , some individuals do experience overt sensations of pain when observing it in others (Osborn and Derbyshire, 2010; Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012),. The source of such inter-individual difference in vicarious experience remains unknown. To explore this question, the current set of studies contrasts people who report experiencing the pain of others against the more typical scenario of those who do not. Whilst the latter participants could be construed as having an implicit simulation of pain, this notion is controversial as it relies on an assumption of reverse inference (i.e. inferring mental operations from brain activity). Crucially, our approach does not hinge on this assumption as we ask participants to report their state rather than infer it in this way.

Prior findings indicate that observing pain results in brain activity in neural regions that partial overlap with those involved in experiencing first-hand pain. Moreover, the central processing of first-hand experience of pain takes place in a widely distributed and nonexclusive network of regions known as the ‘pain matrix’ (Rütgen *et al.* 2015; Melzack 1999; *for critical response see* Iannetti and Mouraux 2010). The primary and secondary somatosensory cortices and the posterior insula have been associated with the processing of the sensory qualities of pain and regions such as the cingulate cortices and the anterior insula have been associated with its affective processing. Functional magnetic resonance imaging (fMRI) findings have shown that the perception of pain (or empathy for pain) also involves activity within this network (Lamm *et al.* 2011). This is most commonly linked to brain activity within the anterior insula and mid-cingulate, but the somatosensory cortices are also recruited when body parts are observed in pain, as opposed to simply knowing about the presence of pain. Further evidence for the involvement of sensory processes in vicarious pain has been provided by electrophysiological

(EEG) and non-invasive brain stimulation findings showing the suppression of neural activity, known to emanate from sensorimotor cortex, during the observation of pain (Avenanti *et al.* 2006; Bufalari *et al.* 2007; Martinez-Jauand *et al.* 2012; Cheng *et al.* 2008; Yang *et al.* 2009).

While of clear importance, these influential studies have not considered whether individuals are consciously experiencing the pain of others or not, despite other research showing that consciously experienced vicarious pain may be as common as 15-30% (Osborn and Derbyshire, 2010; Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012), and are linked to different profiles of brain activity when observing pain in other people (Osborn and Derbyshire, 2010). The studies, however, have been limited in a number of important ways. The cut-off score on the screening procedures are arbitrary and, hence, the prevalence rates themselves are not independently derived. Finally, qualitative differences in the nature of conscious vicarious pain perception (e.g. ‘stinging’, v. ‘wincing’) have not been used to discriminate people. The novel approach taken here addresses these issues by using a data-driven approach (a k-means cluster analysis, Zhang *et al.* 1996) such that the diagnostic cut-off (hence, prevalence) and the groupings reflect the individual differences inherent in the data rather than being set by the experimenter.

Why is it that some people might report conscious vicarious pain experiences and for others do not? There are several possibilities. One is that the same neural mechanisms are used for both groups of individuals but that, in the case of conscious vicarious perception, the level of activity exceeds a threshold for perceptual awareness (so-called Threshold Theory, *see* Ward and Banissy 2015). Another possibility is that different regions within the pain matrix discriminate between these different modes of vicarious perception (de Vignemont 2012). For instance, the sensory regions of the pain matrix may be crucial for conscious vicarious pain (Osborn and Derbyshire, 2010). A final possibility is that it is regions outside of the pain matrix (i.e. that do not normally respond to physical pain) that underpin this difference. In addition to shared representations, recent accounts of empathy highlight the importance of mechanisms for discriminating self and other (to avoid self-other confusion), which determines whether feeling states are attributed externally or internally (Decety and Jackson’s, 2004; Bird and Viding, 2014). This has frequently been linked to the right temporo-parietal junction (rTPJ). This region

may provide flexibility in terms of the degree of vicarious perception that takes place (e.g. resulting in a greater vicarious pain response to racial in-groups, Avenanti *et al.* 2010) and a disruption of this cognitive flexibility may result in an over-reliance on shared representations and a tendency to consciously experience the pain of others (so-called Self-Other Theory, Ward and Banissy 2015). The rTPJ has a particularly important role to play in embodiment: tDCS stimulation of this region can lead to a reduced tendency to imitate (Santiesteban *et al.* 2012), and disturbed body ownership (Tsakiris *et al.* 2008), including out-of-body experiences (Blanke *et al.* 2005).

The current studies aim to identify, characterise and profile conscious vicarious pain and to assess the neurological basis of this experience using a multi-method approach. Study 1 presents evidence for three qualitatively different forms of vicarious pain perception using a new measure, the VPQ (Vicarious Pain Questionnaire) along with a two-step cluster analysis to produce data driven groups based on VPQ responses. Study 2 examines vicarious pain in the sensorimotor cortices observed via suppression of EEG oscillations in vicarious pain groups identified by the VPQ. The ~10Hz rolandic alpha (μ) and ~20Hz rolandic beta (beta) oscillations have been associated sensorimotor activity (Pfurtschuller and Lopes, 1999; Ritter *et al.* 2009) and are a commonly used marker for studies on the neural correlates of vicarious pain perception (Cheng *et al.* 2008; Yang *et al.* 2009). The novel question here is whether prior findings linking cortical oscillations with vicarious pain perception (found in non-differentiated samples; e.g. Cheng *et al.* 2008; Yang *et al.* 2009) are limited to one or more groups, rather than reflective of a population-level characteristic. This question will be further addressed by modelling the results of these previous studies data in light of our own EEG findings. Finally, Study 3 assesses structural differences in the brains of our three groups using voxel-based morphometry (VBM) on grey matter volume (Ashburner and Friston 2000). Our hypothesis is that conscious vicarious pain perception will be linked reductions in grey-matter volume in the rTPJ, alongside differences in regions of the pain matrix that code the affective (e.g. dorsal anterior cingulate cortex, anterior insula) and sensory (e.g. somatosensory cortex) properties that characterise each sub-type.

Materials and Methods:

Study 1: The vicarious pain questionnaire and two-step cluster analysis.

Participants: Vicarious pain questionnaire (VPQ)

The sample was comprised of 573 individuals who had who had not previously been assessed for vicarious pain experiences (Age: 18-60yrs, M=20.37, SE= 0.181, SD= 4.32; Gender: 134 male, 438 female). Participants from this initial pool agreed to be contacted again for future research (Studies 2 and 3). Consent for the study was provided in accordance with the approved ethical review of the project carried out by the University of Sussex (C-REC).

Materials & procedure: VPQ

The VPQ was run using Bristol Online Survey[®] and was adapted from the technique used by Osborn and Derbyshire (2010).

The main body of the questionnaire had participants view 16 videos of people experiencing pain. They were edited to be 10 seconds in duration, these videos using the following link: <https://www.youtube.com/channel/UCT8goTgWGRsu14NjVaPCSGw/videos> .

After each video participants were asked questions about their experience of watching the video. Participants were initially asked whether they experienced a sensation of pain in their own body when viewing the video (yes/no). If participants answered ‘yes’ they were asked three further questions: (1) how intense their pain experience was (1-10 likert, 1= very mild, 10= intense pain); (2) to indicate the localization of their experience (either ‘localised to the same point as the observed pain’, ‘localised but not to the same point, and ‘a general/ non-localisable pain experience’); and (3) to select pain adjectives from a list which best described their experience (descriptors selected from the McGill Pain Questionnaire (Melzack, 1975): 10 sensory, 10 affective & 3 cognitive, *see supplementary methods for examples*). All participants (regardless Q1 answer) were asked to rate how unpleasant they found the experience of viewing the video (1-10 likert, 1= neutral, 10= extremely unpleasant). The end of the questionnaire also included dispositional items (e.g. empathy) and items relating to daily experiences of vicarious pain (*see supplementary methods*).

VPQ: Two-step cluster analysis design

A two-step cluster analysis was performed (Zhang *et al.* 1996). This analysis clusters participants into groups based on their responses to number of input variables from the VPQ. Once completed the analysis produces cluster centroids and categorises participants into the cluster in which they fit best.

The cluster analysis initially involved a hierarchical cluster analysis using Ward's method (Ward, 1963) followed by a non-hierarchical k-means analysis with 50 iterations. The cluster centroids and number of clusters for the k-means analysis were guided by the hierarchical analysis. The two-step approach is considered more suitable for large datasets as it produces relatively inconsistent results whilst avoiding arbitrary selection of initial centroids in an independently run k-means analysis.

Three variables of interest were selected as input variables for the cluster analysis:

- 1) Total pain response (TPR): The total number of conscious vicarious experiences across all video observations (0-16).
- 2) Localised-general: The total number of localised experiences minus the total number of non-localisable experiences.
- 3) Sensory-affective: the total number of sensory descriptors used minus the total number of affective descriptors used.

The level of multi-collinearity between these variables was low.

Results and summary:

A two-step cluster analysis was used to produce the VPQ clusters (Zhang *et al.* 1996). At step 1, observation of the dendrogram indicated a three cluster solution using a Euclidean distance measure of $d=10$ and generated initial cluster centroids that were carried forwards to Step 2. Step 2 (k-means) provided final cluster centroids for the three groups and completed the final group classification of participants.

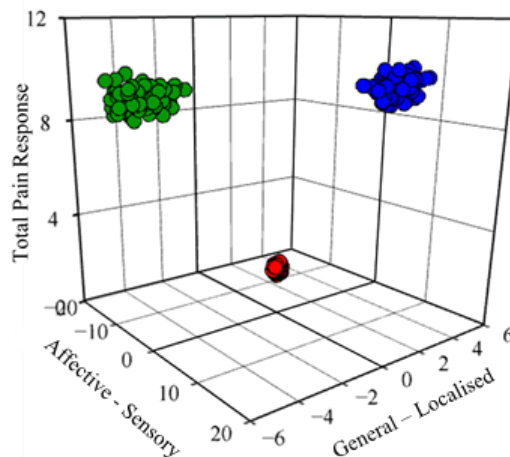
The clusters included a non-responder group ($n=393$), who reported few, if any, conscious experiences of pain. The remaining two groups reported high levels of consciously experienced pain (the two groups did not differ on TPR) but formed a dissociation on localised-general and sensory-affective dimensions. The first of these were 'affective/general group', ($n=68$; 11.9% of participants tested), who displayed an increased use of affective pain descriptors and less tendency to localise. The second group were 'sensory/localiser group, ($n=111$; 19.4% of participants tested), who displayed a

tendency for sensory descriptor use and to localise their experiences to a point on their bodies (*see figure 1* for the bootstrapped cluster means).

There was no difference in age across the groups but there was a disproportionate amount of females in the vicarious pain groups ($\chi^2(391) = 11.510, p = 0.003$, *See supplementary table 1* VPQ demographics). When corrected for 50/50 gender distribution our prevalence estimates are as follows; 16.8% for sensory-localiser vicarious pain responders 10.4% for affective-general vicarious pain responders, and 72.9% for the group reporting no conscious vicarious pain. This represents the first bias-free estimate of prevalence for conscious vicarious pain perception, and the first evidence for two qualitatively different sub-types. In addition the two pain responder groups reported being more empathic, reported experiencing vicarious pain in daily life, and reported being more sensitive to physical pain (but the two groups did not differ on these measures; *See Supplementary Figure 2*).

These three groupings was assessed in terms of whether they predict neural functioning (Study 2) and brain structure (Study 3) even when these subsequent studies were conducted many months later (range 2-18 months).

Figure 1: Bootstrapped resampled means for sensory/localised responders (blue), affective/general responder (green) and no conscious experiences of pain (red). High values on 'total pain response' indicates a high number of vicarious experiences during the questionnaire. Positive values on 'sensory-affective' indicates increased use of sensory descriptors and positive values on 'localised-general' indicates increased localised experiences. The method randomly selects 100 participants, with replacement, and then performs a cluster analysis and computes the cluster means. The procedure is repeated 100 times per condition. Based on Sui and He (2012).



Study 2: Somatosensory oscillations during pain and no-pain observations.

Participants:

Forty participants (Age: mean=23.27, SD=6.04; 18 males, 22 females) were recruited via the online questionnaire. The sample included: 20 non-responders, 10 affective/general responders and 10

sensory/localizer responders (identified from Study 1). The study was reviewed and approved by the University of Sussex's (C-REC) Ethics Committee.

Experimental Stimuli:

Stimuli for the EEG experiment were a series of 128 color images (600x450p) depicting hands and feet in painful (64 images) and non-painful situations (64 images). The images have been used in previous research (including Cheng *et al.* 2008, Yang *et al.* 2009, Jackson *et al.* 2005) and each was displayed twice in the current experiment (256 images).

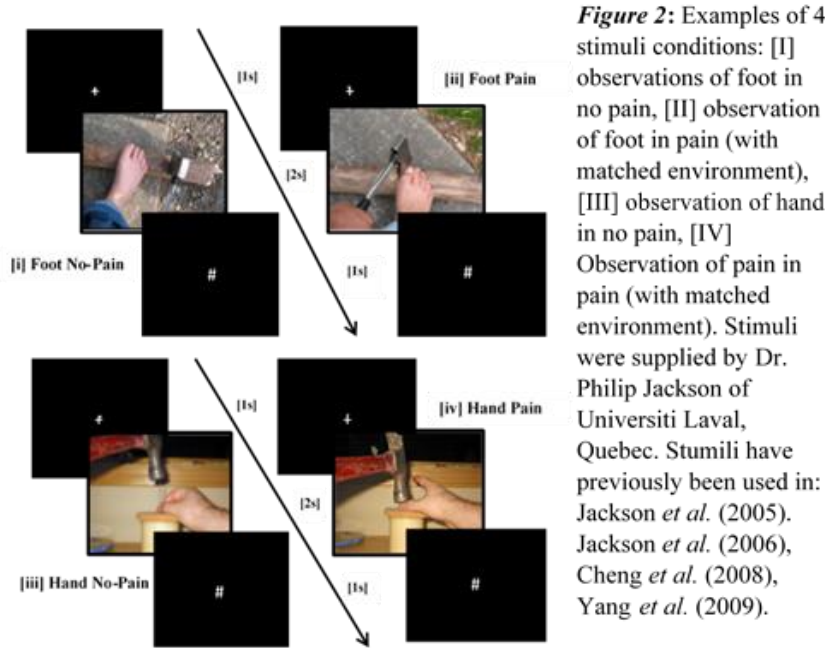
Apparatus:

Two Dell OptiPlex 745 PCs with Windows Vista OS were used for data collection and data recording; stimuli was presented on a 19" Dell LCD monitor (75Hz refresh rate). A Nebraskan synamp² system, amplifier and a Neuroscan cap (standard 10-10 placement system) was used for data collection. Neuroscan 4.3 software was used for recording and Eprime version 2.0 was used for stimuli presentation. All EEG processing and analysis were computed on Matlab 2014b using the EEGLab plugin (<http://sccn.ucsd.edu/eeqlab/>).

EEG Procedure:

Once the EEG cap was applied, there were two sections to the experiment. The first was the baseline recording session in which resting and movement EEG oscillations were observed. Resting mu rhythms were recorded by asking participants to remain still with their palms facing up on their laps and movement recording was produced by self-regulated clenching movements (Pineda, 2005).

The second stage of the experiment involved passive observation of the pain and no pain images. The 256 trials were blocked in eight sets of 32 images, lasting approximately 2.5mins. The trial blocks either contained 32 pain images or 32 no pain images and the order of the blocks were randomized. Presentation of each trial began with a 1s fixation cross [+], followed a 2s stimuli presentation display and finished with a 1s hashtag presentation, (see *figure 2 for stimuli examples*).



EEG Data Acquisition and processing:

Twenty-one channels were recorded over the somatosensory and motor cortices (FCz,FC1,FC3,FC5,FC2,FC4,FC6,CZ,C1,C3,C5,C2,C4,C6,CPZ,CP1,CP3,CP5,CP2,CP4,CP6) as well as two bipolar ocular electrodes either side of the eyes, vertically above and below the right eye and two mastoid electrodes. The impedance was set at 5k Ω .

Offline, the sampling rate was adjusted to 500 Hz, a bandpass filter of 0.1-30Hz was applied, and epochs were extracted -200-2000ms after onset of the stimuli. Channels were then re-referenced to mastoid electrodes, eye blinks were removed via visual inspection and a threshold of +/- 50mv was used to eliminate artefacts and abnormal data.

Fast Fourier transform (3 0.5 wavelet cycles, -200-0 baseline corrected) was computed in an 4-75Hz frequency range to epoch data over a 0-2000ms post stimuli time window to event related spectral permutation data. Suppression values were produced by computing ratios for the power of each experimental condition relative to pre-stimulus baseline.

Analysis of somatosensory mu rhythm and beta oscillations was undertaken from electrodes C3, CZ and C4, which area known to be reliable locations for sensorimotor oscillations (Pineda, 2005). The three electrodes were interpolated to produce averaged time-frequency event related spectral permutations, relative to a 200ms pre-stimuli baseline, for pain and no pain observations.

Results and Summary:

Our hypothesis is that the conscious vicarious pain groups will demonstrate greater mu/beta suppression than controls, and that this will be particularly true of the sensory/localiser groups because we assume that their experiences derive from sensori-motor brain regions linked to mu/beta suppression. The final analysis included 18 Controls (Gender: 11 Females, 7 Males; Age: 23.722, S.E: 1.15), 8 Sensory/Localiser Responders (Gender: 4 Females, 4 males; Age: 25.571, S.E: 1.571) 7 Affective/General Responders (Gender: 4 Females, 3 Males; Age: 23.500, S.E: 1.822). Three participants were excluded for technical errors (triggers not recorded), three for a high rate of trials with artefacts (>50%), and one for having very noisy data (from visual inspection).

Two 2 (condition: pain vs. no-pain) x 3 (group: VPQ groups) mixed ANOVAs were carried out for both frequency ranges. Participant's age and gender were added as covariates of no-interest. We are interested in whether there is a general trend for suppression (as assumed by others) or whether this is limited to one or more groups (as would be revealed by an image * group interaction).

The ~10Hz mu-alpha oscillations ANOVA revealed a borderline significant main effect of image type, $F(1,30)=2.589$, $p=.119$, $r=.343$, and a borderline significant main effect of group, $F(2,31)=2.820$, $p=.077$, $r=.509$. However the analysis did reveal a significant interaction of image type* group $F(2,30)=4.387$, $p=.022$, $r=.710$. (Note that the presence/absence of a main effect of group is not directly relevant to the conclusions as we are interested in how the groups differ when contrasting pain v. no-pain, rather than group differences per se).

A similar pattern of effects was shown for the ~20Hz beta oscillation ANOVA with no significant main effects being shown for image type, $F(1,31)=2.608$, $p=.118$, $r=0.345$, or group, $F(1,31)=1.269$, $p=.297$, $r=.253$. However a significant interaction of image*group was displayed, $F(2,30)=6.115$, $p=.004$, $r=.882$. In both cases the interaction was driven specifically by suppression of synchronisation to the stimuli depicting pain for the sensory-localiser group (see *figure 3* for summary). Within group between planned comparisons showed that the sensory/localiser group were the only group to show differences in pain vs. no pain conditions and between group comparisons showed this

group displayed higher suppression than the other two (*see supplementary results for details*). Bayesian statistics can be used to assess the sensitivity of statistical tests; for example, to determine whether a null result reflects a true null result versus insensitivity (e.g. due to being underpowered). A Bayes factor $p(H_0/Data) > 3$ implies rejection of the null hypothesis and a Bayes factor $p(H_0/Data) < 1/3$ implies acceptance of the null hypothesis. A value in between implies insensitivity (Dienes, 2014). The Bayes analysis was carried out using an online calculator (Dienes 2014) and priors were determined using a previous EEG mu suppression study (Yang *et al.* 2009). There was evidence for the null hypothesis, when contrasting pain and no-pain for the non-responders (for both mu, $p(H_0/Data) = 0.33$, and beta, $p(H_0/Data) = 0.29$). This is an important piece of evidence because the dominant view in the social neuroscience literature is that suppression of these oscillations when observing pain is the neurotypical response. We cast doubt on this view because our non-responders (with the most ‘neurotypical’ profile) do not show this effect but, instead, it is found in the sensory-localised group. Additionally, the affective general group showed Bayes analysis showed was insensitivity for the mu/alpha band and a sensitive null for the beta band (for both mu, $p(H_0/Data) = 1.22$, and beta, $p(H_0/Data) = 0.29$). Critically, the sensory/localiser group show highly sensitive and significant using conventional and Bayesian statistical approaches (for both mu/alpha $p(H_0/Data) = 32.98$, and beta, $p(H_0/Data) = 162.10$). Additionally, despite the small sample size in this group, we see it at the level of individual participants (see Supplementary Results) that there are clear differences in the patterns of EEG responses relative to the other two groups.

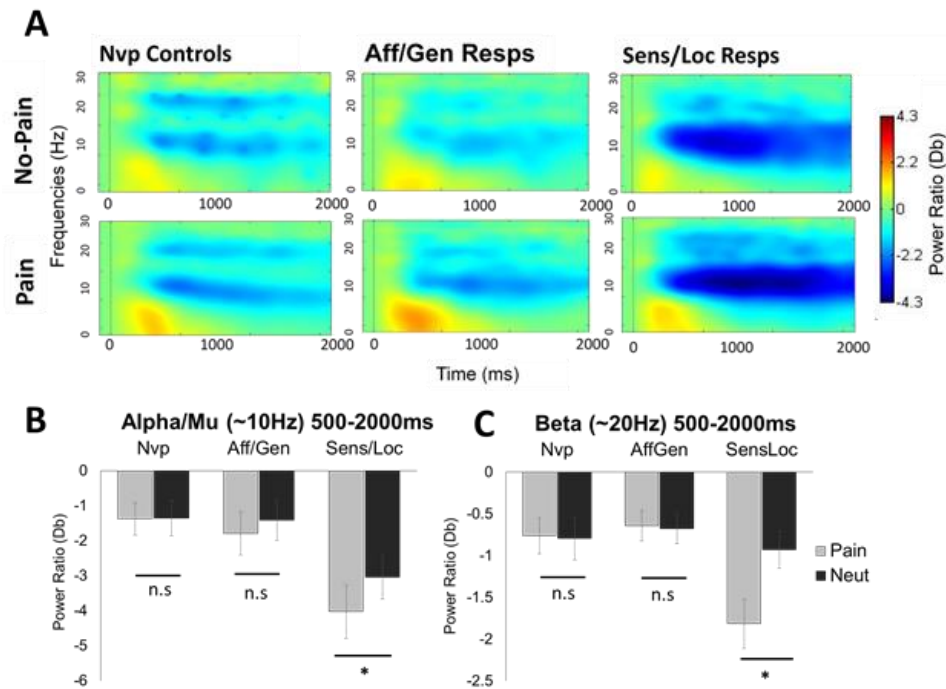
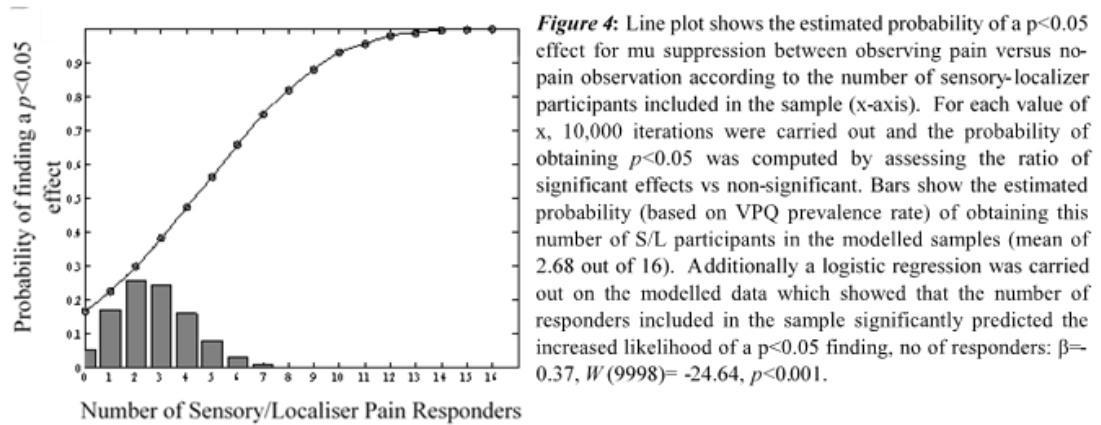


Figure 3: Analysis of somatosensory mu rhythm and beta oscillations was undertaken from electrodes C3, CZ and C4, using 10-20 standard placement system, which area known to be reliable locations for sensorimotor oscillations due to their placement above the post-central gyrus [50]. The three electrodes were interpolated to produce averaged time-frequency event related spectral permutations, relative to a 200ms pre-stimuli baseline, for pain and no pain observations [A]. Pain and No-pain image observations were analysed over 500-2000ms post-stimuli onset, 0-500ms data was not analysed as this period was likely to reflect voltage fluctuations related to ERP waveforms produced by stimuli onset[Martinez-Jauand, *et al.* 2012]. Two frequency ranges were observed, each with an ANOVA bar graphs presented; [B] ~10Hz mu alpha range (8-13Hz) and [C] ~20Hz beta oscillation range (18-22Hz).

To assess

whether previous demonstrations of vicarious pain mu suppression in the general populations may have been influenced by the presence of sensory/localiser group (Cheng *et al.* 2008, Yang *et al.* 2009) we modelled the previous results of Cheng *et al.* (2008) which had 16 participants shown pain and neutral images. The model varied the number of sensory/localiser participants included in the analyses and we show that the likelihood of $p < 0.05$ is drastically increased by the inclusion of sensory/localiser participants. As few as 4/16 sensory/localiser participants gives a ~50% chance of obtaining a significant ($p < 0.05$) result.



Group differences in alpha and beta suppression was also assessed during the hand movement task to investigate whether observed effects were due to underlying group differences in somatosensory oscillations (rather than vicarious perception in particular). All groups display suppression of alpha/mu oscillations (over the C3 scalp position) during hand movement and differences were observed between the groups ($F(2,29) = 3.745, p = 0.036$, $r = .638$). However these effects did not mirror the group differences observed in the image observation analysis as post hoc (Bonferroni corrected) tests displayed that the A/G responders ($M = -1.66$, $S.E. = 0.25$) showed increased suppression relative to S/L Responders ($M = -0.56$, $S.E. = 0.41$; $p = 0.041$) but not controls ($M = -1.11$, $S.E. = 0.166$, $p = 0.307$), no effects were observed between S/L Responders and Controls ($p = 0.441$). No groups effects were observed over the C3 Scalp position for beta oscillations ($F(2,29) = 0.638$, $p = 0.535$, $r = .327$). That is, differences in mu and beta suppression for the sensory-localised group during vicarious pain perception do not reflect differences in these frequencies across all measures (such as physical movement). Moreover, the vicarious pain results are consistent with sensori-motor mu suppression rather than with visually-based alpha desynchronization because the effects were significantly greater over central electrodes than the adjacent frontal and posterior electrodes; a pattern that was also found for actual hand movements that can be directly linked to sensori-motor activity (*see supplementary results for details*).

In summary, the results of Study 2 provide confirmatory evidence of the validity of the distinctions in vicarious pain perception identified in Study 1: i.e. differences in subjective report are reflected in differences in brain activity assessed at a later time point. They suggest a link between

sensory-localised vicarious pain and mu/beta suppression but raise doubts about whether mu/beta suppression are a good measure of ‘mirroring’ processes in the wider population. We establish this by showing a sensitive null result for the non-responder group (using a sample size comparable with previous research, N=18) and by showing a significant group X pain/no-pain interaction that is driven by a significant effect in the sensory-localised group.

Study 3: Structural differences based on subjective of vicarious pain (Voxel-based morphometry, VBM).

Participants:

Ninety-three individuals were recruited for the VBM analysis however 9 participants were excluded because of outdated T1 scanning sequences, resulting in 84 participants in the analysis (Age: 18-39 yrs, M=24.17, SE= 0.54, SD= 9.17; Gender: 48 male, 36 female). The sample included 51 controls (Gender: 26 Females, 25 Males; Age: M=23.450, S.E= 0.54), 17 sensory/localiser responders (Gender: 8 Females, 9 Males; Age: M=24.882, S.E.=1.254) and 16 with affective/general responders (Gender: 9 Females, 7 Males; Age: M=25.687, S.E: 1.781). Recruitment was primarily driven by opportunistic sampling from participants who already had a T1 scan (resulting in more non-responder controls), but was augmented by purposive sampling to increase the N of the rarer groups. The project was approved by the Brighton and Sussex Medical School Research Ethics and Governance Committee.

MRI data acquisition: VBM

Participants were placed in a supine position in a Siemens Avanto (Brighton, England) 1.5 T MR scanner. A T1-weighted MPRAGE interleaved sequence (TR = 2730ms, TE = 3.57ms, FOV = 240 x 256 x 192 mm, voxel size=1x1x1 mm) was used to acquire structural MR images.

MRI data processing:

Processing of T1-weighted images for voxel-based morphometry was undertaken using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) with the VBM8 toolbox (<http://www.neuro.uni-jena.de/vbm/download/>) on Matlab 2014b. Initially MR tissue segmentation was computed using the default parameters on SPM8’s ‘new segment’ tool. VBM normalisation processes were carried out using the default options for the ‘estimate and write’ function on VBM8 toolbox, thereby creating grey

and white matter templates using DARTEL algorithms, and then normalizing the participant images to MNI space using the previously created templates. This was followed by spatial smoothing, FWHM=8mm x 8mm x 8mm. The smoothing kernel size was used as we had no specific hypotheses about the variability, as a result the default SPM kernel size was used. Two participants were excluded from the analysis due to a lack of homogeneity of covariance (Ashburner and Friston 2000).

MRI data analysis:

The VBM data was analysed using a General Linear Model with the pain groups variable acting as the variable of interest (Controls vs. S/L responders vs. A/G responders) and 3 variables of no interest including: Age, Gender and Intracranial volume (ICV). Particular attention was given to contrasts between S/L responders vs. Controls and A/G responders vs. Controls, and the conjunction analysis between these two contrasts. Initially a whole brain $p < 0.05$ FWE corrected was used to threshold the data. An ROI analysis was also carried out using small volume correction (SVC) based on four ROIs which include [1] bilateral dorsal anterior cingulate cortex ($x = -2$, $y = 23$, $z = 40$), [2] bilateral anterior insula (Left: $x = -40$, $y = 22$, $z = 0$; Right: $x = 39$, $y = 23$, $z = -4$), [3] bilateral primary and secondary somatosensory cortices (anatomical maps from SPM anatomy tool box), [4] right temporo-parietal junction ($x = 57$, $y = -52$, $z = 14$). MNI locations for ROIs 1 and 2 were based on Lamm's *et al.* (2011) meta-analysis of vicarious pain and used a 10mm spherical mask, ROI 3 used full anatomical maps of SI+SII taken from SPM8's anatomy toolbox (Eickhoff *et al.* 2007) and ROI 4 was based on Krall's *et al.* (2015) meta-analysis of the rTPJ, again using a 10mm spherical mask. The ROI analysis was correction for multiple comparisons by using a $p < 0.05$ FWE cluster threshold correction.

Results and summary:

Initially, we compared grey matter volume differences between our three groups using a whole brain analysis. Although a number of regions displayed effects at $p < 0.001$ (uncorrected) no regions showed significant effects at the $p < 0.05$ (FWE corrected) threshold. Following this an ROI analysis (one-way ANOVA across groups followed by planned contrasts), using the 4 previously mentioned ROIs with small volume correction (SVC). Figure 5 shows the whole-brain results (left) and ROI results (right). Several significant differences were found between controls and the two responder groups, but

direct comparisons between A/G and S/L groups revealed no significant effects across either whole brain $p < 0.05$ (FWE corrected) or a SVC ROI $p < 0.05$ (FWE corrected) threshold.

GM volume effects overlapping with the ‘pain matrix’:

During the ROI analysis the sensory/localiser group displayed significantly increased grey matter volume relative to controls in the left anterior insula ($t(1,78) = 4.64, p = 0.014$) and right anterior insula cortex ($t(1,78) = 4.04, p = 0.007$). S/L Responders also showed increased grey matter volume relative to controls in the right, primary somatosensory cortex, in area 3b ($t(1,78) = 4.47, p = 0.02$).

The affective/general group displayed increased GM matter volume in the left anterior insula cortex ($t(1, 78) = 3.95, p = 0.026$) and a borderline significant effect over the right somatosensory cortex area 3b ($t(1,78) = 3.74, p = 0.06$).

A conjunction analysis was computed on the S/L responders > Controls and A/G responder > Controls comparisons which showed significant conjunction at the $p < 0.001$ (uncorrected) threshold over the left anterior insula and the right primary somatosensory cortex, area 3b.

GM volume effects in regions implicated in self/other processing:

During the ROI analysis the S/L responders also displayed significantly reduced grey matter volume, relative to controls, in the right anterior temporo-parietal junction ($t(1,78) = 3.76, p = 0.001$) and the A/G responders showed significantly decreased GM volume, relative to controls, in a small portion of the right anterior temporo-parietal junction ($t(1,78) = 3.37, p = 0.031$). A conjunction analysis showed significant (surviving $p = 0.05$ FWE correction) overlap between the Controls > S/L responders and Controls > A/G responders in the right anterior temporo-parietal junction ($t(2,78) = 3.37, p = 0.031$). See figure 5 for ROI effects in the rTPJ.

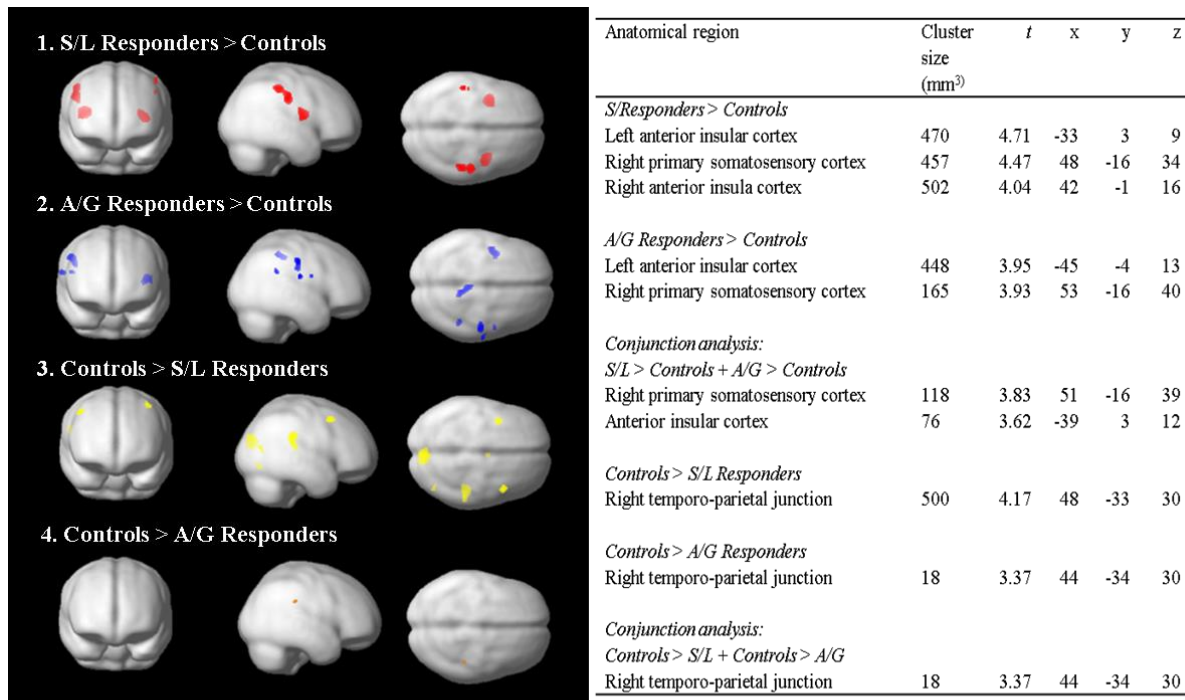


Figure 5: T1 weighted structural MRI images were entered into a one-way ANCOVA model with the three cluster groups entered as the main variable of interest; age, gender and inter-cranial Volume (ICV) were added as covariates for the model. Planned t-contrasts between each of the two responder groups and controls were assessed for volumetric GM differences and can be identified as follows: [Red] regions which display increased GM in S/L responders relative to controls, [Blue] areas in which S/L responders display decreased GM volume relative to controls, [Yellow] areas in which Controls display increased GM volume compared with S/L responders, [Orange] Areas which Controls showed increased GM volume relative to A/G responders. Rendered images shows whole comparisons using a $p < 0.001$ whole brain analysis. The table shows significant ROI effects at $p < 0.05$ FWE ($k=10$) using the previously described ROIs. In addition group contrasts the table also displays two conjunction analysis using a $p < 0.05$ FWE corrected ($k=10$) showing overlap effects for [1] S/L responders > Controls + A/G > Controls, [2] Controls > S/L Responders + Controls > A/G Responders. MNI coordinates, MRI images & GM volume bar charts are displayed for each effect which survived thresholds.

Study 3 provides further confirmatory evidence for the distinction between qualitatively different forms of vicarious pain perception, identified in Study 1, notably between those who report conscious vicarious pain and those who do not. Although the two responder groups (sensory-localised v. affective-general) did not differ in our VBM analysis, we predict that such differences will be found on functional measures (see Study 2), behavioural measures, and/or using other forms of structural imaging (e.g. white-matter connectivity).

Discussion:

Prior work has highlighted evidence for a shared system involved in perceiving and experiencing first-hand pain (or empathy for pain). This work has commonly been conducted on healthy young adult participants, and rarely addressed inter-individual variability in the extent to which people “feel” vicarious pain. Using a new measure, the VPQ, and cluster analysis we document, for the first

time, that there are two distinct forms of conscious vicarious pain perception in addition to a more typical non-responder sub-type. One sub-type is characterised by sensory pain descriptors and a tendency to localise pain on the body (this is linked to suppression of sensorimotor EEG mu and beta oscillations when observing pain). A second sub-type is characterised by affective pain descriptors, and the vicarious pain is not-localised to a specific part of the body. Importantly, both types of conscious vicarious pain perception are linked to reduced grey matter in the right temporal-parietal junction (rTPJ). This region is not normally linked to pain perception, but is central to both social cognition and bodily self-consciousness (Blanke *et al.* 2015). Both types are also linked to increased grey matter in regions involved in pain perception (anterior insula, primary somatosensory cortex) as well as other aspects of brain-body interaction more broadly. The non-responder subtype could be characterised as an absence of vicarious pain or an implicit/unconscious form of vicarious pain. Our results cannot distinguish between these possibilities, although the field as a whole tends to assume an implicit simulation of the pain of others (see Lamm's *et al.* 2011; and for a contrary view see Iannetti and Mouraux 2010).

Although previous research has reported conscious vicarious pain perception to be surprisingly common (Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012), there has been little consensus as to how to measure it and, hence, the current estimates of prevalence are unreliable. Our approach of using a data driven two-step k-means cluster analysis has enabled this question to be addressed without imposing arbitrary cut-offs. The results reveal a prevalence of conscious vicarious pain of 27%, further divisible into the two sub-groups. The results also indicate that females are over represented in these groups, by a factor of nearly 2:1. The reasons for this are unknown, but it is consistent with the finding that mu suppression when observing pain, tends to be greater in females (Yang *et al.* 2009). fMRI studies have not consistently revealed a greater activity in pain-related regions in females when watching others in pain (Lamm *et al.* 2011), but there is evidence that females modulate their vicarious pain less than men according to social context (Singer *et al.* 2006). These previous findings need to be revisited in light of our research to determine if they are driven by the presence of one or both types of conscious vicarious pain rather than reflecting a true difference between genders.

More broadly, our results suggest that measures of mu/beta suppression in response to observing pain may not be a reliable neurotypical measure of ‘mirroring’ brain activity as noted also by others (Hobson and Bishop, in press). Our results show a sensitive null result in the non-responder group. Although our sample size is smaller, we show that the suppressions effects are present in the sensory-localised responder group (including at the individual level) and we mathematically model how this could give rise to significant results in a sample that does not take into account individual differences in vicarious pain.

Further, our research demonstrates that vicarious pain is not a unitary construct, as is commonly assumed in the literature, but exists in qualitatively different varieties in terms of both subjective experiences of pain and in terms of structural and functional differences in the brain. Based on our results we suggest two mechanisms that contribute to conscious vicarious pain perception: one relating to sensorimotor resonance and one relating to self-other discrimination. These are considered in turn.

Firstly, there is a greater involvement of sensorimotor processes in those people who report sensory/localiser vicarious pain, showing increased suppression of both mu-alpha and beta oscillations. The suppression of mu-alpha and beta frequency ranges are both known to be present when privately experienced physical somatosensory experiences occur, with suppression of mu-alpha oscillations is associated with somatosensory processes and nociception whilst suppression of beta is more associated with voluntary action and proprioception (Pfurtscheller, 1999; Ritter *et al.* 2009). Furthermore, similar occurrences of these alpha and beta suppression patterns which participants view touch and pain (Cheng *et al.* 2008; Yang *et al.* 2009). Additionally, the VBM results show that a number of regions involved in the private processing of pain display grey matter volume increases relative to controls. Most notable of these effects was increases in grey matter within primary somatosensory cortex, (with its somatotopic representation of the body) and in the anterior insula cortex, both central regions in the processing of affective and sensory qualities of personally experienced pain (Payron *et al.* 2000) and vicariously processed pain (Lamm *et al.* 2011; Osborn and Derbyshire 2010). We predicted that the affective/general group may have structural differences in affective regions of the pain matrix (e.g. insula), whereas the S/L group may have greater somatosensory cortical differences. This was not

found and others have queried the validity of this affective-sensory division of pain networks (Iannetti *et al.* 2010). Instead the VBM data suggests that S/L responders and A/G responders display similar structural brain differences (albeit of a greater magnitude in the S/L group) which may account for their conscious experiences of vicarious pain. Further differences between the S/L and A/G subtypes may be found on functional measures (as in the previous EEG results) or using other structural measures (e.g. of white matter).

Secondly, both vicarious pain groups had less grey matter density in the TPJ region. This region is a key hub within the ‘social brain’ implicated in mental state attribution (Decety and Lamm, 2007), altruism (Morishima *et al.* 2012), and embodiment and attentional processes (Krall *et al.* 2014). Of particular interest in the current study is the rTPJ’s role in self-other discrimination, specifically body-based representations (Decety and Sommerville, 2003; Brass *et al.* 2009; Banissy *et al.* 2009). In the case of conscious vicarious pain it may be that they are unable to properly monitor and control for representations of other people’s bodily states resulting in a tendency for ‘other’ representations being incorporated in to self-processing thereby resulting in activation of shared representations for pain (Ward and Banissy, 2015; Sowden and Shah, 2014). In one study examining spontaneous perspective taking, it was found that vicarious pain groups were more likely to spontaneously adopt a third-person perspective as opposed to the typical egocentric bias (Derbyshire *et al.* 2013). We speculate that this may be a common behavioral profile of both sub-types of conscious vicarious pain that is linked to individual differences in the TPJ. Recent meta-analyses of the rTPJ have divided the region into anterior and posterior sections (Bzdok *et al.*, 2013; Krall *et al.*, 2014). Our VBM differences are centered on the anterior rTPJ and it is noteworthy that this region has strong functional connectivity with regions such as mid-cingulate and anterior insula implicated in bodily perception, including, but not limited to pain (Bzdok *et al.*, 2013).

The findings from the sensory-localiser group resemble those reported for a rarer group of individuals (mirror-touch synesthetes, MTS) who report feeling tactile sensations on their own body when watching neutral (i.e. non-painful) touch on others (Avenanti *et al.* 2006; Fitzgibbon *et al.* 2012; Banissy *et al.* 2009). This is linked to activity in primary and secondary somatosensory cortex when

watching touch (assessed through fMRI rather than EEG) and also reduced grey matter volume in the rTPJ (Holle *et al.* 2013). Furthermore recent behavioral findings have shown that people with MTS are inhibited in controlling representations of other people, a process known to be associated with the rTPJ (Santiestiban *et al.* 2015). It would be interesting to know whether this S/L vicarious pain group are also more likely to report vicarious sensations when observing non-painful touch.

Conclusions:

In conclusion, the vast majority of studies on empathy for pain have assumed that vicarious pain is not linked to reportable pain-like sensations/feelings. Those who have looked at conscious vicarious pain responses have not developed systematic ways of quantifying or characterising it. The present research not only offers a new tool (the VPQ), it offers a new conceptualisation of vicarious pain into three groups characterised by differences in phenomenology and differences in brain structure and function. We show that differences in subjective accounts of vicarious pain perception differ across individuals that it is manifested in somatosensory mirroring (for sensory/localizer responders) and differences in self/other processing.

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Supplementary methods:

Vicarious Pain questionnaire:

All videos of pain presented to the participants can be found at the following URL:

<https://www.youtube.com/channel/UCT8goTgWGRsu14NjVaPCSGw/videos>.

[Section1]After each video participants were asked the following questions (note: questions labelled with ‘*’ were only asked if participants responded with a ‘yes’ to quest 1):

1. Did you experience any bodily sensation of pain whilst observing the person in pain?
2. Please rate how painful this experience was for you (Likert scale, 1= Very Mild Pain, 10= Highly intense pain). *
3. Did you feel this pain in a specific location or was it a more general bodily feeling? *
 - a. General bodily experience
 - b. Localised to the same point as the observed pain.
 - c. Localised but not to the same point as the observed pain.
4. How unpleasant did you find the experience of watching this video? (Likert scale 1= not unpleasant, 10= Highly unpleasant)
5. Looking back on your experiences of vicarious pain please choose any of the following adjectives to describe the type of pain you experience. (Select as many as you feel necessary

to describe your past experiences or experience of watching the videos). [Note: these were presented as a random list to participants and not grouped in this way] *

Table 1: Full list of response questionnaire pain descriptor responses present in the VPQ.

Sensory Descriptors:	Affective Descriptors	Cognitive Evaluative Descriptors
Tingling	Nauseating	Brief
Stinging	Aversion	Constant
Sharp	Wincing	Rhythmic
Dull	Fearful	
Soreness/Aching	Terrifying	
Stiff/Tight	Sickening	
Shooting	Torturing	
Throbbing	Gruelling	
Burning	Vicious	
Numbness	Suffocating	

In addition to the video based questions, participants were also asked a number of single item dispositional questions [Section 2]. The wording for these is as follows:

1. Would you say you have a high or low physical pain threshold? i.e., highly sensitive to pain or not very sensitive to pain. (1=no at all sensitive to pain, 10= highly sensitive to pain).
2. Do you consider yourself an empathetic person? (1= not at all empathetic, 10= highly empathetic).
3. Do you consider yourself an emotionally sensitive person? i.e. are you easily upset? (1= Not emotional, 10= highly emotional)
4. Are you made uncomfortable by the sight of, your own or another person's, blood? (1= No discomfort, 10=absolute discomfort).

Participants were also asked to questions about their past experiences with vicarious pain [Section 3]:

These items are as follows (note: questions labelled with “*” were only asked if participants responded with a ‘yes’ to question 1):

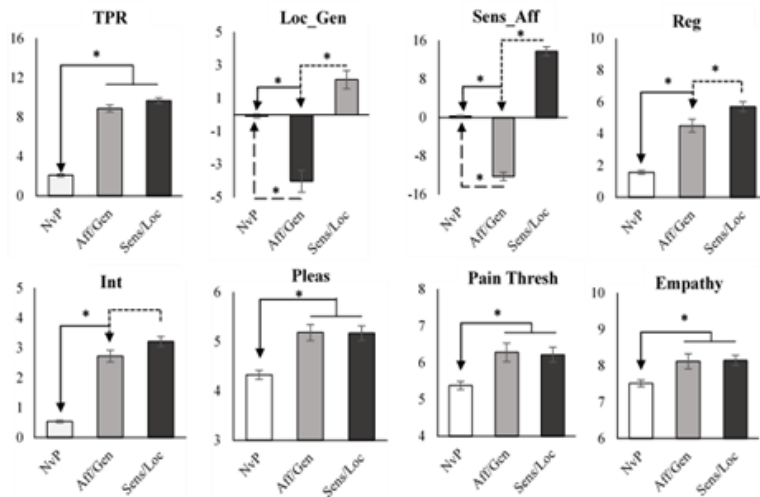
1. Have you ever noticed feeling a sensation of pain whilst observing another in pain in your past or everyday life?
2. How regularly do you experience vicarious pain? (0= hardly ever, 10= very regularly) *
3. Do you feel as if you vicarious pain experiences are helpful, or a hindrance to your everyday life? (-5=hindrance, 5=helpful) *
4. Do you experience vicarious pain more for loved ones/ friends or is it an indiscriminate sensation (i.e. happens for everyone you see in pain)? (1= Happens for everyone, 10= only happens for loved ones).*
5. Based on your the description for pain synaesthesia given at the beginning of this questionnaire and your experience of watching the videos, do you feel as if you may potentially have pain synaesthesia (note: participants were given a short description of vicarious pain synaesthesia before this item)?

Supplementary Results:

Study 1: The Vicarious Pain Questionnaire (VPQ)

Table 2: Demographics of participants based on groups. Gender is cross tabulated with cluster group, observed frequencies are presented with percentages brackets. Mean age is represented for each group with standard error in brackets.

		Controls	Aff/Gen Responders	Sens/Loc Responders
Gender	F:	286 (65.29)	57 (13.01)	95 (21.68)
	M:	108 (80.59)	10 (7.46)	16 (11.94)
Age		20.15 (0.19)	20.88 (0.47)	20.79 (0.73)



Supplementary Figure 2: Displays bar graphs for a variety of variables on the vicarious pain questionnaire (see Supplementary methods for VPQ for question wording of these items/measures). TPR=Section 1, Question 1; Loc_gen= Section 1, Question 3; Sens_aff= Section 1, Question 5; Reg = Section 3, Question 2; Int = Section 1, Question 2; Pleas = Section 3, Question 4; Painthresh: Section 2, Question 1; Empathy= Section 2, Question 2.

Study 2: Planned comparisons for EEG suppressions Mixed ANOVAs:

Within group planned contrasts for the ~10Hz mu-alpha and ~20 Hz rolandic-beta oscillations showed that only the sensory/localiser group displayed significantly greater suppression during pain observations relative to no-pain (mu-alpha: sensory/localiser= *pain* = -4.03, *no-pain*=-3.04, $t(7)= 3.35$, $p=0.015$, $d=1.184$), Controls= $t(17)=0.11$, $p=0.911$, $d=0.026$, affective/general = $t(6)=1.61$, $p=0.152$, $d=0.608$. beta: sensory/localiser= *pain*= -1.82, *no-pain*=-0.93, $t(7)=3.81$, $p=0.009$, $r=d=1.347$; controls= $t(17)=0.21$, $p=0.84$, $d=0.049$, affective/general: $t(6)=0.16$, $p=.877$, $d=0.060$). Between groups planned comparisons for pain and neutral images showed that sensory/localiser displayed increased mu suppression for pain observations relative to both groups and across both frequency ranges (Mu-alpha: S/L>A/G $p=0.04$, S/L> Controls $p=0.01$; rolandic-beta: S/L>A/G $p=0.02$, S/L>Controls $p=0.01$). No significant effects were observed in A/G vs. controls across any comparisons.

Study 2: Analyses of EEG electrode clusters

We aimed to establish that the mu/beta oscillations that we observe (both during vicarious perception and when performing movements) are consistent with a sensori-motor origin by showing that they are maximal over central sites relative to neighbouring sites. A source analysis was not possible without more electrode coverage. We assessed the difference between mu and beta oscillations between the central (somatosensory) electrodes (C3+CZ+C4), the frontal electrodes (CF3+CFZ+CF4) and posterior electrodes (CP3+CPZ+CP4). For this analysis pain and no-pain condition were collapsed across one another as the current analysis focused on the origin of the oscillations rather than difference between the image conditions. A one-way repeated measures ANOVA was carried across the three positions (Frontal vs. Central vs. Posterior) for both alpha and beta oscillations. For alpha oscillations there was a significant effect of electrode position, $F(2,45.316)=7.851$, $p=0.003$, $r=.873$ (Greenhouse-Geisser). Post-hoc comparisons showed that the central electrode positions ($M=-1.94$, $S.E.=0.36$) differed significantly from both the frontal electrode positions ($M=-1.45$, $S.E.=0.34$; $t(31)=5.734$, $p<.001$) and posterior electrodes ($M=-1.52$, $S.E.=0.29$; $t(31)=2.653$, $p=.012$) and that there was no differences between frontal and posterior electrodes ($t(31)=0.469$, $p=.64$). Across the beta channel the one-way ANOVA revealed no differences between the 3 electrode positions ($F(2, 45.11)=0.084$, $p=.911$, $r=.64$; Greenhouse-Geisser). Furthermore, alpha and beta oscillations were observed during the hand movement task which showed a similar pattern scalp distribution to the image observation task. For the alpha frequency band a borderline significant one-way ANOVA effect was observed, $F(2,62)=2.957$, $p=.059$. Post hoc tests showed that the central alpha band displayed the greatest mu suppression ($M=-1.24$, $S.E.=0.15$) when compared with the posterior channels ($M=-0.92$, $S.E.=0.11$; $t(31)=-3.202$, $p=.003$) and a borderline significant difference compared with frontal channels ($M=-0.95$, $S.E.=0.20$, $t(31)=1.706$, $p=.098$), no effect was observed between frontal and posterior electrodes ($t(31)=0.17$, $p=.863$). The beta oscillations showed a significant one-way ANOVA effect, $F(2, 62)=3.338$, $p=.044$, $r=.600$, with central electrodes ($M=-0.95$, $S.E.=0.09$) showing increased suppression relative to posterior electrodes ($M=-0.76$, $S.E.=0.11$; $t(31)=2.76$, $p=0.009$), but not frontal electrodes ($M=-0.88$, $S.E.=0.09$; $t(31)=0.99$, $p=0.326$) and no effect was observed between frontal and posterior electrodes ($t(31)=1.46$, $p=.15$). As the data from the image

observations and hand movement show a similar pattern, with central electrodes displaying the maximal mu suppression (rather than posterior electrodes), it is unlikely that the observed suppression in alpha and beta oscillations originate from an occipital (visual alpha) source and are more likely to display somatosensory processing.

Figure Legends

Figure 1: Examples of 4 stimuli conditions: [I] observations of foot in no pain, [II] observation of foot in pain (with matched environment), [III] observation of hand in no pain, [IV] Observation of pain in pain (with matched environment). Stimuli were supplied by Dr. Philip Jackson of Universiti Laval, Quebec. Stimuli have previously been used in: Jackson *et al.* (2005). Jackson *et al.* (2006), Cheng *et al.* (2008), Yang *et al.* (2009).

Figure 2: Bootstrapped resampled means for sensory/localised responders (blue), affective/general responder (green) and no conscious experiences of pain (red). High values on ‘total pain response’ indicates a high number of vicarious experiences during the questionnaire. Positive values on ‘sensory-affective’ indicates increased use of sensory descriptors and positive values on ‘localised-general’ indicates increased localised experiences. The method randomly selects 100 participants, with replacement, and then performs a cluster analysis and computes the cluster means. The procedure is repeated 100 times per condition. Based on Sui and He (2012).

Figure 3: Analysis of somatosensory mu rhythm and beta oscillations was undertaken from electrodes C3, CZ and C4, using 10-20 standard placement system, which area known to be reliable locations for sensorimotor oscillations due to their placement above the post-central gyrus [50]. The three

electrodes were interpolated to produce averaged time-frequency event related spectral permutations, relative to a 200ms pre-stimuli baseline, for pain and no pain observations [A]. Pain and No-pain image observations were analysed over 500-2000ms post-stimuli onset, 0-500ms data was not analysed as this period was likely to reflect voltage fluctuations related to ERP waveforms produced by stimuli onset [Martinez-Jauand *et al*, 2012]. Two frequency ranges were observed, each with an ANOVA bar graphs presented; [B] ~10Hz mu alpha range (8-13Hz) and [C] ~20Hz beta oscillation range (18-22Hz).

Figure 4: Line plot shows the estimated probability of a $p < 0.05$ effect for mu suppression between observing pain versus no-pain observation according to the number of sensory-localizer participants included in the sample (x-axis). For each value of x, 10,000 iterations were carried out and the probability of obtaining $p < 0.05$ was computed by assessing the ratio of significant effects vs non-significant. Bars show the estimated probability (based on VPQ prevalence rate) of obtaining this number of S/L participants in the modelled samples (mean of 2.68 out of 16). Additionally a logistic regression was carried out on the modelled data which showed that the number of responders included in the sample significantly predicted the increased likelihood of a $p < 0.05$ finding, no of responders: $\beta = -0.37$, $W(9998) = -24.64$, $p < 0.001$.

Figure 5: T1 weighted structural MRI images were entered into a one-way ANCOVA model with the three cluster groups entered as the main variable of interest; age, gender and inter-cranial Volume (ICV) were added as covariates for the model. Planned t-contrasts between each of the two responder groups and controls were assessed for volumetric GM differences and can be identified as follows: [Red] regions which display increased GM in S/L responders relative to controls, [Blue] areas in which S/L responders display decreased GM volume relative to controls, [Yellow] areas in which Controls display increased GM volume compared with S/L responders, [Orange] Areas which Controls showed increased GM volume relative to A/G responders. Rendered images shows whole

comparisons using a $p < 0.001$ whole brain analysis. The table shows significant ROI effects at $p < 0.05$ FWE ($k=10$) using the previously described ROIs. In addition group contrasts the table also displays two conjunction analysis using a $p < 0.05$ FWE corrected ($k=10$) showing overlap effects for [1] S/L responders > Controls + A/G > Controls, [2] Controls > S/L Responders + Controls > A/G Responders. MNI coordinates, MRI images & GM volume bar charts are displayed for each effect which survived thresholds.

Supplementary Figure 1. Supplementary effects in Vicarious Pain Questionnaire based on

cluster analysis grouping: Displays bar graphs for a variety of variables on the vicarious pain questionnaire (see Supplementary methods for VPQ for question wording of these items/measures).

TPR=Section 1, Question 1; Loc_gen= Section 1, Question 3; Sens_aff= Section 1, Question 5; Reg = Section 3, Question 2; Int = Section 1, Question 2; Pleas = Section 3, Question 4; Pain thresh: Section 2, Question 1; Empathy= Section 2, Question 2.

Supplementary Table 1. Vicarious Pain questionnaire pain Descriptors: Full list of response questionnaire pain descriptor responses present in the VPQ

